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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/908,867	08/08/97	YOUNG A	227/166

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HM12/0709

EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	13

DATE MAILED: 07/09/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/908,867	Young et al.
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *Jan 15, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) *12-19* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11, 20, and 21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to comply with sequence rules

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Informalities in the drawings are indicated on the enclosed PTO-948.

Acknowledgment is made of the amendments to Figure 1 in Paper No. 7, filed September 11, 1998. The proposed amendments to the Figure 1 were not entered. As indicated above, when the application is allowed, formal drawings will be required.

Election/Restriction

2. Applicant's election with traverse of Group I, claims 1-11 and 20-21, in Paper No. 7, filed September 11, 1998, is acknowledged. Applicant's further election of species in Paper No. 10, filed January 15, 1999 is also acknowledged. The traversal to the restriction requirement is on the ground(s) that no serious burden would be imposed on the examiner if the groups were to be rejoined. Applicant points to the fact that all of the groups are classified in 514/2. This is not found persuasive because the methods of groups 1-VII are different in objective and endpoints, response variables and criteria for success. Proper examination of these inventions will require

consideration of issues other than and in addition to searches in the Patent shoes and the non-patent literature. It is noted that Applicant has pointed to no errors in the restriction requirement.

Applicant's argument for withdrawing the election of species requirement is found persuasive and all species of Group I, 1-11 and 20-21, will be examined.

The restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-21 are pending.

Claims 12-19, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1-11 and 20-21 are examined on the merits.

Sequence Rules

4. This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claims 20 and 21 refer to sequences which do not have specific identifiers and which are not included in the sequence listing. Applicant is required to submit a new sequence listing and a computer readable form (CRF) which includes the sequences recited in claims 20 and 21. Applicant must also submit a statement indicating that the paper and computer readable copies are the same.

APPLICANT IS GIVEN THE RESPONSE PERIOD OF THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Objections

5. Claims 20 and 21 are objected as not complying with 1.821(d) of the Sequence Rules and Regulations. When the description or claims of a patent application discusses a sequence, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-11, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites an incomplete method. It is not clear how administration of an exendin or exendin agonist will result in "beneficial regulation of gastrointestinal motility".

Claim 1 is vague and indefinite in the recitation "therapeutically effective amount". There is no definition of what constitutes a therapeutically effective amount in the specification.

Claim 9 is vague and indefinite in the recitation "said gastric motility" which is a species of "gastrointestinal motility". Since claim 9 depends from claims 1, 2 or 3, the recitation should be to the genus of "gastrointestinal motility" of claim 1 and not to the species, "gastric motility", of claim 2.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 20 and 21 are drawn to methods of regulating gastrointestinal motility comprising administering an exendin agonist that is selected from a peptide compound formula. It appears that SEQ ID NOS: 5-35 are 30 embodiments of this formula.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention,; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The specification teaches how to make 30 embodiments of the formulas recited in claims 20 and 21. The specification also teaches that exendin-3 and exendin-4 delay gastric emptying (informal Figure 2 and Table I). Thus, there is support in the specification for a method using either exendin-3 or exendin-4 to delay gastric emptying. However, claims 20 and 21 specifically exclude the use of exendin-3 and exendin-4. The specification also teaches the use of exendin-4 analogs, specifically, exendin-4 acid and ^{14}Leu, ^{25}Phe exendin-4 (SEQ ID NO: 5) (Figure 3 and Table II). However, the specification does not teach the use of any other of the 30 embodiments or any of the other possible embodiments that are encompassed by the sequence formulas of claims 20 and 21. Thus, the specification provides inadequate guidance for the use of most of the possible exendin analogs encompassed by claims 20 and 21. The specification provides no

guidance to one of skill in the art on which substitutions of exendin-3 or exendin-4 would result in compounds useful in a method for regulating gastrointestinal motility. Given the breadth of claims 20 and 21, the lack of guidance in the specification as to why specific substitutions, especially with uncommon amino acids, one of skill in the art cannot practice the claimed invention commensurate with the scope of the claims without undue experimentation and with a reasonable expectation of success.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Dupre et al (Dupre, J. et al. Diabetes, 44: 626-630, 1995) as evidenced by either Goke et al (Goke, R. et al. J. Biol. Chem., 268(26): 19650-19655, 1993) or Rai et al. (Rai, A. et al. Am. J. Physiol., 265: G118-G125, 1993).

Claims 1-3 are drawn to methods of regulating gastrointestinal motility comprising administering exendin or an exendin agonist. The regulation of the gastrointestinal motility may comprise reducing gastric motility (claim 2) or comprise delaying gastric emptying (claim 3).

Dupre et al teach that truncated glucagon-like peptide I (GLP-I, GLP-I(7-36)amide) has been shown to retard gastric emptying of food in normal humans (see abstract and page 628, first column). As evidenced by Goke et al and by Rai et al, truncated GLP-I binds to the same receptor as do exendin-4 (Goke et al and Rai et al) and exendin-3 (Rai et al). Therefore, by definition, GLP-I is an exendin receptor agonist. Thus, Dupre teaches a method of delaying gastric emptying (and therefore of regulating gastric motility and of gastrointestinal motility) that is the same as that claimed.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dupre et al (supra) in view of Rai et al (supra).

Claims 4 and 5 are drawn to methods of regulating gastrointestinal motility (reducing gastric motility or delaying gastric emptying) wherein the exendin is exendin-3 (claim 4) or exendin-4 (claim 5).

As discussed above, Dupre et al teach a method of delaying gastric emptying comprising administering GLP-I. Dupre et al do not teach the method using exendin-3 or exendin-4. However, Rai et al teach that exendin-3 and -4 are potent exendin receptor agonists that are much 10 fold more potent than GLP-I (see page G124, first column, 2nd paragraph (Rai refers to GLP-I as TGLP-1)). Thus, it would have been obvious to one of skill in the art at the time the invention was made to have substituted either exendin-3 or exendin-4 for GLP-I in the method of delaying gastric emptying taught by Dupre et al. One would have been motivated to make the substitution because the use of a more potent agonist would reduce the required dose and thus would be expected to have fewer side-effects. One would have had a reasonable expectation of success because exendin-3, exendin-4 and GLP-I are agonists of the same receptor.

14. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dupre et al (supra) in view of either Chernish et al (U.S. Patent 3,862,301, Chernish, S.M. et al., published January 21, 1975) or Kolterman et al (WO 95/07098, Kolterman, O. et al., published March 16, 1995) and further in view of Eng (U.S. Patent 5,424,286, Eng, J., published June 13, 1995) .

Claims 6-8 are drawn to methods of regulating gastrointestinal motility in a subject undergoing a gastrointestinal diagnostic procedure (claim 6); the procedure may be a radiological examination (claim 7) or magnetic resonance imaging (claim 8).

The teachings of Dupre et al have been discussed above. Neither Dupre et al teach a method of regulating gastrointestinal motility in a subject undergoing a gastrointestinal diagnostic

procedure. However, Chernish et al disclose a method of reducing gastrointestinal motility during gastrointestinal diagnostic procedures such as X-ray radiography and fluoroscopy (see column 1, lines 53-62). Chernish discloses that the purpose of inhibiting gastrointestinal motility is to gain better visualization of pathologic conditions (column 1, lines 18-21). Chernish does not disclose a method where the diagnostic procedure is magnetic resonance imaging. However, magnetic resonance imaging is an obvious variation of a radiological examination and in some cases may be preferred because magnetic resonance imaging is a procedure that does not require the use of radioisotopes. Absent evidence to the contrary, there is no reason that the method of Chernish may not be used in a patient undergoing magnetic resonance imaging.

Kolterman et al also disclose methods comprising the administration of pharmaceutical agents which reduce gastric motility in patients undergoing gastrointestinal radiologic examinations. A disclosed example of a pharmaceutical agent is glucagon. Thus, it is well known in the art to pharmacologically induce gastric hypomotility for the facilitation of gastrointestinal diagnostic procedures. Therefore, it would have be obvious to one of skill in the art to combine the teachings of Chernish et al or of Kolterman et al with that of Dupre et al to make the claimed invention. One would have been motivated to substitute an exendin agonist such as GLP-I for glucagon because GLP-I may disrupt fuel metabolism less than does glucagon. Eng discloses that the metabolic actions (insulinotropic) of GLP-I and exendins are glucose-dependent (column 1, lines 49-68 and column 2, line 53-57). Glucagon, which is a hyperglycemic agent, and may cause

hyperglycemia as a side effect of being used to inhibit gastric motility whereas, GLP-I (or exendins) would only cause a decrease in glycemia if the subject was already hyperglycemic.

15. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dupre et al (supra) in view of Daniel et al (Daniel, O. et al. British Medical Journal, 3: 720-722, 1974) and further in view of Eng (supra).

Claims 9-11 are drawn to methods of regulating gastrointestinal motility wherein the gastrointestinal motility is associated with a gastrointestinal disorder (claim 9). The gastrointestinal disorder may be a spasm (claim 10) or one of the following disorders: acute diverticulitis, a disorder of the biliary tract or a disorder of the Sphincter of Oddi (claim 11).

The teachings of Dupre et al and Eng have been discussed above. Dupre et al do not teach a method applied to subjects with a gastrointestinal disorder such as a spasm or any of the above-recited species of a spasm. However, Daniel et al teach a method of treating spasm (acute diverticulitis, page 720, first column, 2nd paragraph) that is the administration of an agent known to reduce intestinal motility, glucagon. Given that Eng teaches that exendins and GLP-1 may be metabolically safe and that Daniel teaches that a side-effect of glucagon administration is occasional nausea and vomiting, it would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Dupre et al with that of Daniel et al and Eng to make the claimed invention. One would have been motivated to substitute GLP-I for glucagon in the method of Daniel for the reasons given above in the discussion of claims 6-8.

Advisory Information

16. No claims are allowed. Claims 20 and 21 appear to be free of the art. Claims 20 and 21 were searched to the extent that was possible given that the formulas of claims 20 and 21 were lacking a specific sequence identifier and could not be searched using sequence searching algorithms.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzel, Ph.D. can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
July 6, 1999

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER

Application No. 08/908,867

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] 7An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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